

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR RESEARCH RESOURCES**

**NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL
MINUTES OF MEETING
JANUARY 19, 2005**

The National Advisory Research Resources Council convened for its 129th session at 8:30 a.m. on Wednesday, January 19, 2005, in Conference Room 10, Building 31. Dr. Judith L. Vaitukaitis, Director, National Center for Research Resources (NCRR), National Institutes of Health (NIH), presided as Chair. The meeting was open to the public until 1:00 p.m., at which time it was closed to the public for the review, discussion, and evaluation of grant applications as provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of Public Law 92-463.

COUNCIL MEMBERS PRESENT

Dr. Stephen W. Barthold
Dr. Wah Chiu
Dr. Kenneth G. Cornetta
Dr. Randall E. Dalton
Dr. Machi F. Dilworth
Liaison Member, NSF
Dr. Mark H. Ellisman
Dr. Catherine C. Fenselau
Dr. James G. Fox

Dr. Roland F. Hirsch
Liaison Member, DOE
Dr. Joan S. Hunt
Dr. Gwen A. Jacobs
Dr. Cynthia E. Keppel
Dr. Thomas G. McGuire
Dr. Monte Westerfield
Ms. Sheila C. Zimmet
Dr. Stuart M. Zola

COUNCIL MEMBERS ABSENT

Dr. Robert J. Beall
Col. (Dr.) Peter Demitry
Dr. Kelly D. Garcia

Dr. Eon Nigel Harris
Dr. John E. Maupin, Jr.
Dr. Paul G. Ramsey

SPECIAL INVITED GUESTS FOR OPEN SESSION

Dr. P. Michael Conn, Associate Director and Senior Scientist, Oregon National Primate Research Center; Special Assistant to the President, Oregon Health and Science University (OHSU); Professor of Physiology and Pharmacology and Cell and Developmental Biology, OHSU
Dr. Stacey B. Gabriel, Director, Genetic Analysis Platform, The Eli & Edyth L. Broad Institute, Massachusetts Institute of Technology
Dr. Margaret J. McFall-Ngai, Visiting Professor, Department of Medical Microbiology and Immunology, UW Symbiosis Cluster, University of Wisconsin, Madison
Dr. Carl A. Pinkert, Professor, Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry
Dr. Ann E. Pulver, Professor of Psychiatry and Director of the Epidemiology - Genetics Program in Psychiatry, Johns Hopkins School of Medicine
Dr. Edward G. Ruby, Professor, Medical Microbiology and Immunology at the University of

Wisconsin, Madison
Dr. Bruce C. Trapnell, Associate Professor of Medicine and Pediatrics, University of Cincinnati
College of Medicine and Chair, Steering Committee, Rare Diseases Clinical Research
Network (RDCRN)
Dr. Pamela L. Zeitlin, Professor of Pediatrics, Department of Pediatrics, Johns Hopkins
University

STAFF OF OTHER NIH COMPONENTS

Dr. Stephen C. Graft, NIH/ORD
Ms. Lora Kutkat, NIH/OD/OSP
Dr. Margaret D. Snyder, OSA/OD/NIH
Dr. Giovanna M. Spinella, NIH/ORD

OTHERS PRESENT

Mr. Stephen J. Heinig, Senior Staff Associate, Division of Biomedical and Health Sciences
Research, Association of American Medical Colleges, Washington, D.C.
Mr. Eugene Isaac, Constella Group
Ms. Sherry A. Marts, Society for Women's Health Research

OPEN SESSION

I. Call to Order: Dr. Judith L. Vaitukaitis, Director, NCRR

Dr. Judith Vaitukaitis welcomed Council members and guests to the 129th meeting of the National Advisory Research Resources Council. She announced that the following Council members would not be present: Dr. Robert J. Beall, Dr. Eon Nigel Harris, Dr. John E. Maupin, Jr., Dr. Paul G. Ramsey, Col. (Dr.) Peter Demitry, and Dr. Kelly D. Garcia. Dr. Vaitukaitis acknowledged the invaluable service of the following retiring Council members: Drs. Stephen W. Barthold, Eon Nigel Harris, Gwen A. Jacobs, and Monte Westerfield.

II. Consideration of Minutes: Dr. Judith L. Vaitukaitis, Director, NCRR

The minutes of the Council meeting held on September 9, 2004, were approved as written.

III. Future Meeting Dates: Dr. Judith L. Vaitukaitis, Director, NCRR

The next Council meeting will be held on Thursday, May 19, 2005.

IV. Personnel Update: Dr. Judith L. Vaitukaitis, Director, NCRR

DHHS Personnel

Robert W. Hosenfeld, Director of NIH's Office of Human Resources, accepted a new position with the Department of Health and Human Services, Program Support Center in

December 2004. Mr. Hosenfeld played an intricate role in the recent consolidation of the HR functions at NIH. Ms. Christine Steyer, Deputy Director of the Office of Human Resources, will serve as Acting Director until that position is filled.

NIH Personnel

The NIH community mourns the loss of Dr. John R. La Montagne, Deputy Director of the National Institute of Allergy and Infectious Diseases (NIAID). Dr. La Montagne died suddenly in Mexico City on November 2, 2004, at the age of 61. He devoted his life to improving the health of children and adults here and abroad. His NIH career spanned more than 30 years, and his leadership and counsel have been invaluable in NIH research efforts to fight emerging and re-emerging diseases.

Dr. David A. Schwartz was appointed as the new Director of the National Institute of Environmental Health Sciences and the National Toxicology Program by NIH Director Dr. Elias A. Zerhouni, effective April 2005. Prior to his appointment, Dr. Schwartz served as Director of the Pulmonary, Allergy, and Critical Care Division, and Vice Chair of Research in the Department of Medicine at Duke University.

Dr. David B. Abrams was appointed as the Associate Director for Behavioral and Social Sciences Research and Director of the Office of Behavioral and Social Sciences Research by Dr. Zerhouni in December 2004. Prior to his appointment, Dr. Abrams was Professor of Psychiatry and Human Behavior, Professor of Community Health and Co-director of Transdisciplinary Research at Butler Hospital, Brown Medical School. Dr. Abrams also is the founding Director of Brown's Centers for Behavioral and Preventive Medicine, at The Miriam Hospital.

Dr. Lana R. Skirboll, Associate Director for Science Policy, OD, was designated as the NIH Liaison to the Food and Drug Administration (FDA) by Dr. Zerhouni in December 2004. Dr. Skirboll will serve as Zerhouni's principal representative, as well as the NIH point of contact, for matters of joint concern to NIH and the FDA.

NCRR Personnel

Dr. Franziska B. Grieder was named Associate Director of NCRR's Division of Comparative Medicine (DCM) in December 2004. Since 2000, Dr. Grieder has managed the DCM's Laboratory Animal Sciences Program, under which she created the Mutant Mouse Regional Resource Centers Program and supervised grants related to mammalian models, comparative and functional genomics, and training opportunities for veterinarians and veterinary students.

Ms. Lori A. Mulligan was appointed as Director of NCRR's Office of Science Policy and Public Liaison in January 2005. Ms. Mulligan returns to NCRR from the NIAID, where she held the position of Biodefense Research Coordinator. Ms. Mulligan has worked at

NIH for over 12 years, having spent 3 years with the National Cancer Institute and 8 years with NCRR.

Dr. Charles G. Hollingsworth, former Director of NCRR's Office of Review, returned to NCRR in December 2004 from the Center for Scientific Review where he established the Aging Systems and Geriatrics Study Section. Dr. Hollingsworth has been with NIH for over 23 years. Now a Health Scientist Administrator in the Division of Research Infrastructure, he will be working with the Institutional Development Award Program, specifically the grants from the Centers of Biomedical Research Excellence.

V. Legislative and Budget Updates: Dr. Judith L. Vaitukaitis, Director, NCRR

The FY 2005 Consolidated Appropriations Bill was passed by Congress and signed by the President on December 8, 2004. The total NIH funding for FY 2005 is \$23.8 billion. The Consolidated Appropriations Bill provided NCRR with \$1.1 billion, after rescissions. The construction program for FY 2005 is at a level of \$29.8 million, down from \$118.5 million in FY 2004.

VI. Rare Diseases Clinical Research Network (RDCRN): Dr. Bruce C. Trapnell, Associate Professor of Medicine and Pediatrics, University of Cincinnati College of Medicine; Chair, Steering Committee, RDCRN

Dr. Bruce Trapnell reported on the Rare Diseases Clinical Research Network (RDCRN). This network was created to develop improved diagnostic methods and treatments for rare diseases by facilitating collaboration and data sharing between investigators, patient support groups, and NIH to improve the lives of individuals with rare diseases. The RDCRN consists of 10 Rare Diseases Clinical Research Consortia (each devoted to a group of rare diseases), a Data and Technology Coordination Center (DTCC), and 34 affiliated patient advocacy groups that have banded together to form the Coalition of Patient Advocacy Groups. The network involves 311 investigators and staff located at 55 medical institutions in the United States and 7 other countries. Clinical research studies will be conducted within 32 NIH-supported General Clinical Research Centers that are associated with the RDCRN.

Forty-one rare diseases are now under study within the RDCRN. Thirty-two clinical protocols are currently in development within RDCRN consortia, and 13 near-term protocols are now under consideration by the newly established Data and Safety Monitoring Board (DSMB). Rare disease clinical protocols under current DSMB review include six longitudinal studies, six phase I or phase II therapeutic trials or outcomes studies, and one study to evaluate a novel diagnostic approach. Several diagnostic tests for rare diseases are now in current use at RDCRN sites, and others are under development. Multiple novel therapeutic approaches for rare diseases will be tested in clinical trials that are expected to be initiated in 2005. The RDCRN vocabulary unit has been instrumental with the assistance of the RDCRN investigators in incorporating standards across networks and developing an adverse event reporting system. The

RDCRN, in collaboration with national standards organizations—including the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), Health Level 7, and the National Library of Medicine—has facilitated the implementation of unique concepts necessary for incorporating standardized rare disease terminology into national vocabularies.

VII. Protein Origami - A New Therapeutic Approach Un-Folding: Dr. P. Michael Conn, Associate Director and Senior Scientist, Oregon National Primate Research Center; Special Assistant to the President, and Professor of Physiology and Pharmacology and Cell and Developmental Biology, Oregon Health and Science University

Dr. P. Michael Conn reported that mutations in the gonadotropin releasing hormone (GnRH) receptor can cause hypogonadotropic hypogonadism (HH). Many of these mutations cause the receptor to fold improperly, and it was previously assumed that the misfolding rendered the receptor itself inactive. Dr. Conn and his colleagues found that by using pharmacoperones (low molecular weight molecules that serve as molecular scaffolding) the mutants would fold correctly, and they could restore full activity compared to the wild-type receptor. This result indicated that the mutant was actually fully functional; however, it misfolded—and therefore misrouted—rendering it unable to function correctly. The researchers showed that the misfolding caused the receptor to be misdirected to a location in the cell where it was degraded. This rescue method works for misfolding that is caused by a variety of genetic mutations.

The researchers received experimental compounds that bind the GnRH receptor from commercial drug companies and screened these chemicals for the ability to rescue the GnRH receptor. They found that several different chemical classes of GnRH antagonist peptidomimetics can rescue the mutated receptors, and that the ability to rescue the receptors is related to the affinity with which the drug binds the receptor.

There are a few genetic mutations that lead to production of receptors that cannot be rescued by these drugs. If one drug rescues a receptor with a particular mutation, then all the drugs will rescue that receptor. If a mutation creates a receptor that cannot be rescued by any one of the compounds, then none of the drugs will restore the activity of that receptor. The scientists believe that the drugs enter the cell and stabilize the receptor protein as it is produced, causing it to fold correctly and be transported to the cell membrane. Since several classes of drugs can restore the activity to a variety of mutated GnRH receptors, there is a strong possibility of finding a drug that will be safe and effective in a broad group of HH patients. Dr. Conn pointed out that there are several other diseases, such as hypercholesterolemia, cystic fibrosis, retinitis pigmentosa, nephrogenic diabetes insipidus, and other neurodegenerative diseases that are caused by misrouted receptors and which may be treated by drugs that stabilize the protein structure.

VIII. Status of the Human Haplotype Map and Implications for Human Disease Research: Dr. Stacey B. Gabriel, Director, Genetic Analysis Platform, The Eli & Edyth L. Broad Institute, Massachusetts Institute of Technology

Dr. Stacey Gabriel reported on activities underway at the NCRR-funded National Center for Genotyping and Analysis at The Eli & Edyth L. Broad Institute, MIT. Starting with the Human Haplotype Map (Hap Map) project, the largest genotyping project ever undertaken, she described the identification of over 300 million genotypes that will validate and identify underlying biological processes that contribute to human disease. Researchers are poised to take advantage of the improved diagnostic and therapeutic approaches that single nucleotide polymorphisms (SNPs) will bring to our understanding of human genetic variations. Investigators may not need to test every DNA sequence variant to understand how they contribute to human disease; a subset might be able to serve as a proxy for all human variation.

The Hap Map project has, to date, involved 10 countries and a budget of \$100 million. Its goals include defining the patterns of genetic variation across the human genome, guiding selection of Single Nucleotide Polymorphisms (SNPs), guiding the selection of proxy variants that might effectively capture variation through the genome, and immediate release of all data to the public with no intellectual property constraints. The outcome has been a huge database of the genotypes in a reference panel of individuals. There are five major technologies used to generate data, with each fulfilling a unique role. Advances have led to substantial cost decreases from over \$0.70 per genotype in 1998 to \$0.002 in 2005. The technology is resource intensive and technically challenging, with rapidly evolving computational and analytic tools. That makes NCRR's investment in the new National Center for Genotyping and Analysis at Broad Institute all the more important, since it allows external investigators access to a fully integrated laboratory and analytic workflow, so that they can conduct genetic studies and leverage Broad Institute's \$6 million in resources. Experiments are expected to begin in the next 6 months.

IX. Progress in the Identification of Genes for Schizophrenia - The Application of New Technology and Shared Resources in a Genetically Isolated Population: Dr. Ann E. Pulver, Professor of Psychiatry, and Director, Epidemiology-Genetics Program in Psychiatry, The Johns Hopkins School of Medicine

Dr. Ann Pulver presented a scientific overview of her ongoing research to better understand the genetic and biological basis of schizophrenia and other related disorders (i.e., bipolar disorder). She reviewed the current status of the search for schizophrenia susceptibility genes and described the scientific design and progress of genetic linkage and association strategies that she and her collaborators have developed. These studies focus on cases drawn from volunteer families from the relatively genetically isolated Ashkenazi Jewish (AJ) population and an anonymous control sample from the same population. Her linkage studies have found specific chromosomal regions likely to harbor schizophrenia susceptibility loci (10q22-q23) in the AJ population, and her association

studies have identified six candidate genes that appear to influence risk for schizophrenia in the AJ population. These results need to be replicated in independent samples, and the genes need to be examined through functional studies. The large AJ case and control samples collected by her group serve as a rich resource for genetic studies of schizophrenia and other psychiatric disorders in the AJ population.

X. Electronic Submission of Grant Applications: Dr. Amy L. Swain, Health Scientist Administrator, Division for Biomedical Technology Research and Research Resources, NCRR

Dr. Amy Swain presented information on NIH's efforts to support electronic submission of grant applications. In 1999, NIH began the electronic Research Administration (eRA) project to replace the paper grant application and related processes with electronic transactions and components. Part of this process requires that grantee institutions have an internal system that is compatible with NIH's eRA system. They can either develop their own system or purchase a service that can do this for them.

Currently, NIH has five cooperative agreements with small businesses that have developed systems to allow submission of electronic grant applications to NIH. Currently, NIH's first focus is on the submission of competing grant applications called the electronic Competing Grant Application Process (eCGAP). It allows applicants to submit data streams through XML and PDF files. The pilot mode for eCGAP has now been completed. As of February 1, 2005, the process is available to anyone who wants to submit R01, R03, or R21 grant applications, as long as they have modular budgets with no consortia or subcontracts. Future developments will expand the process to other grant mechanisms.

XI. A Bacterial Toxin Governs Organ Development in the Squid: Dr. Margaret J. McFall-Ngai, Visiting Professor, Department of Medical Microbiology and Immunology, UW Symbiosis Cluster, University of Wisconsin, Madison

Dr. Margaret McFall-Ngai reported that biologists are becoming increasingly aware that animals, including humans, rely on complex communities of microbial partners for normal health and development. Nevertheless, most research has historically focused on the interactions between microbial pathogens and their hosts. One concept resulting from this focus is that certain common surface molecules of bacteria, such as lipopolysaccharide (LPS) and peptidoglycan (PGN), are perceived by the host as potent toxins and pathogen-recognition factors. The fact that most beneficial and benign bacterial symbionts of host animals share these molecules has presented an apparent paradox. Dr. McFall-Ngai's research on the relatively simple model system, the association between the sepiolid squid, *Euprymna scolopes*, and its luminous bacterial partner, *Vibrio fischeri*, has demonstrated that LPS, PGN, and their derivatives can act as signal molecules that are required for the normal development of host tissues. These findings, and studies of other beneficial animal-microbe associations, are revealing the importance of understanding the basic nature of the normal, healthy relationships

between hosts and their microbial partners. Such stable, highly evolved, and communication-rich relationships are the context into which the pathogen invades.

XII. 2005 Biennial Advisory Council Report - Certifying Compliance With the NIH Policy on Inclusion Guidelines: Dr. Louise E. Ramm, Deputy Director, NCRR

Dr. Louise Ramm outlined NIH's policy and NCRR's compliance with the requirement under the 1993 Revitalization Act to include appropriate numbers of women and members of ethnic and minority groups in all clinical trials. As part of the implementation of the Act, each NIH institute's or center's advisory council is required to prepare a biennial report describing how the institute has complied with this provision of the Act. Dr. Ramm presented a synopsis of NCRR's compliance with the inclusion guidelines. The Council approved NCRR's compliance and the report process.

CLOSED SESSION

This portion of the Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Council members discussed procedures and policies regarding voting and confidentiality of application materials, Committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to that effect.

XIII. Application Review

The Council considered 423 applications and recommended 423 for a total first-year amount of \$200,050,042 (direct costs).

ADJOURNMENT

The Council adjourned at 2:00 p.m. on January 19, 2005.

CERTIFICATION

We hereby certify that, to the best of our knowledge, the foregoing minutes and supplements are accurate and complete.

Dr. Judith L. Vaitukaitis
Chair, National Advisory Research Resources Council

Date

and
Director, National Center for Research Resources, NIH

Dr. Louise E. Ramm
Executive Secretary, National Advisory Research Resources Council
and
Deputy Director, National Center for Research Resources, NIH

Date

These minutes will be formally considered by the Council at its next meeting; corrections or notations will be incorporated into the minutes of that meeting.

Attachment:
Council Roster

NOTE: Open Session materials are available from the Executive Secretary or the Committee Management Office, NCRR.